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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,829	03/07/2006	Fumihiko Ishikawa	4456-0105PUS1	6864

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
08/25/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/560,829	ISHIKAWA ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-24,27 and 34-38* is/are pending in the application.

4a) Of the above claim(s) *5,7,9-24,27,35 and 37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6,8,34,36 and 38* is/are rejected.

7)☒ Claim(s) *1 2 4,6 8,34,36 and 38* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/13/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on June 5, 2009 that includes a response to the Advisory action dated May 7, 2009, and the claim amendment dated April 13, 2009, have been entered. Claims 1, 2, 5-8 and 35-38 have been amended. No claims were cancelled or newly added. Accordingly, claims 1, 2, 4-24, 27 and 34-38 are pending in the application. Claims 9-24 and 27 stand withdrawn from further consideration, with traverse, as drawn to non-elected inventions and species of the invention. Amended claims 5, 7, 35 and 37 are hereby withdrawn from further consideration, as directed to non-elected subject matter (i.e. the non-elected species of NK cells, NKT cells and IgE. The claims have been examined commensurate in scope with the elected species of the invention, i.e. mouse, B and T cells, cord and peripheral blood, and immunoglobulin G.

Claims 1, 2, 4, 6, 8, 34, 36 and 38 are under current examination.

Information Disclosure Statement

The information disclosure statement filed 4/13/2009 is in compliance with 37 CFR 1.98(a); thus the information contained therein has been considered and indicated as such on form PTO/SB/08a.

Response & Maintained Claim Objection

Claims 1, 2, 4-8, 34, 36 and 38 stand objected to for the recitation of a SCID/IL2rg-null mammal (excluding human). The objection previously set forth on p. 3 of the Office action dated January 13, 2009 is maintained for claims 1, 2, 4-8, 34, 36 , and is further applied to instant

claim 38. Although the examination of the instantly claimed invention has been limited to the elected species of mouse, it should be noted that the SCID genotypic designation is reserved for only a few mammals, and is not generally applicable to any mammal. Moreover, the instant specification defines the extended genotypic designation NOD/SCID/IL2rg-null as that of NOD.Cg-*Prkdc*^{scid}IL2rg^{tm1Wjl}/Sz mice. The claims should therefore be amended to recite a NOD/SCID/IL2rg-null mouse.

Applicants state that while the term "NOD" is used specifically for mice, "SCID" is generically applicable to mammals (i.e. rats, rabbits, dogs, pigs and mice). Applicants' arguments have been fully considered, but are not found persuasive.

SCID denotes "severe combined immunodeficiency disease". The instant specification describes immunodeficient mammals (for example, an SCID mouse), p. 7, line 4. The specification further states: "the term immunodeficient mouse is used to mean a severe combined immunodeficiency disease (SCID mouse)" (p. 7, lines 23-24), and separately provides examples of a mammal, that may include mouse, rat, hamster, guinea pig, sheep, pig and monkey (p. 7, lines 20-21). The SCID phenotype (bubble boy syndrome) is a specific form of immunodeficiency and the prior art has only characterized the disease in a few mammalian species. The specification is devoid of any description for the numerous SCID mammalian species claimed (other than mouse), that would include rabbits and dogs, as argued by Applicants.

Thus, the objection is maintained and further applied to claim 38.

Claim Rejections - 35 USC § 112- New Matter/Written Description

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 6, 8, 34, 36 and 38 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art (hereafter the Artisan), that the inventor(s), at the time the application was filed,

had possession of the claimed invention. 37 CFR §1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

The claims include the new limitation of SCID/IL2rg-null mammal. The instant specification is devoid of such description for any of numerous species of mammals. The as-filed specification discloses only the single species of NOD/SCID/IL2rg-null mouse.

Thus, at the time the application was filed, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of any of SCID/IL2rg-null mammal, other than mouse.

MPEP 2163.06 notes: "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

Response to Arguments:

Applicants disagree, and with reference to pages 7 and 8 of the specification, argue that while it is clear that the mouse model is preferred, the immunodeficient mammal of the present invention is not limited to mice, and may include other mammals. Further arguing that the specification provides implicit support and that there is no *haec verba* requirement. Applicants' arguments have been fully considered, but are not found persuasive.

In response, it should be noted that while Applicants have disclosed immunodeficient non-human mammals, such genus is not limited to the SCID/IL2rg-null immune deficiency. The specification only describes a single species of NOD mouse as having the SCID/IL2rg-null

genotype (i.e. carry mutations for combined immune deficiency and IL2 receptor gamma deficiency). Thus, the issue is also one of possession at the time of filing by Applicants. The disclosed single species of mouse is not representative of the numerous mammalian species encompassed by the claims. As the specification discloses only a NOD/ SCID/IL2rg-null mouse, the single species does not constitute a substantial portion of the claimed genus. Applicants' attention is also directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Thus, Applicants have failed to demonstrate possession of the numerous SCID/IL2rg-null mammalian non-human species claimed. Disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 (written description requirement not satisfied by merely providing "a result that one might achieve if one made that invention"); *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming a rejection for lack of written description because the specification does "little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate").

Therefore, the breadth of the claims as reading on numerous species, that have the SCID/IL2rg-null genotype and are further capable of displaying the requisite phenotype, including those yet to be discovered; in view of the level of knowledge or skill in the art at the time of the invention, and the limited information provided in the specification, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of numerous

mammalian species, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied.

Priority

This Application claims the benefit of foreign priority under 35 U.S.C. 119(a)-(d), to Japanese Application 2003-171240 (6/16/2003). However, it is noted that Applicant cannot rely upon the foreign priority papers to overcome any rejection made under 35 USC 102 or 103 because the Application does not appear to contain support for the NOD/SCID/IL2rg-null mouse as claimed in the instant amendment, and a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Response & Maintained Claim Rejections - 35 USC § 103

Claims 1, 2, 4, 5, 8, 34, and 38 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ishikawa et al. (Am. J. Transpl. 2:520-525, 2002), in view of mouse strain NOD.Cg-*Prkdc*^{scid}IL2rg^{tm1Wjl}/Sz (Stock No: 00557, Jackson Laboratory). The rejection set for the on pp. 5-6 of the Office action dated January 13, 2009 is maintained for reasons of record and is re-iterated as follows:

The claims embrace a newborn NOD/SCID/IL2rg-null mouse into which human cord blood hematopoietic cells have been transplanted, and which is able to generate T cells from said human cells.

Ishikawa et al. describe long-term xenogeneic engrafting of cord blood human hematopoietic cells into newborn NOD/SCID/β2-microglobulin deficient mice (Title and Abstract; limitation of claims 1, 4 8, 34 and 35). Further describing multilineage engraftment, and that high levels of engraftment were primarily by T cells (first column, p. 490 and Figure 1). With reference to previously published results by Kollet et al., the authors additionally state because the duration of engraftment was relatively short, backcrossing onto other strains of mice may be needed for longevity, constituting breeding of the immature immunodeficient mouse (limitation of claim 2).

While Ishikawa et al. do not describe their graft recipient mice as NOD/SCID/IL2rg-null, such was known in the prior art. It should be noted that the instant specification indicates that the

NOD/SCID/IL2rg-null mice are NOD.Cg-*Prkdc*^{scid}IL2rg^{tm1Wjl}/Sz, from Jackson Laboratory (Example 6, p. 23).

The product description for stock no. 005557, discloses NOD.Cg-*Prkdc*^{scid}IL2rg^{tm1Wjl}/Sz mice as commercially available from the Jackson Laboratory, and further states that the mice carry mutations for combined immune deficiency and IL2 receptor gamma deficiency, lack mature T cells, B cells and functional NK cells, leading to better engraftment of human hematopoietic stem cells.

The teachings of Ishikawa et al. and Jackson Laboratory product stock no. 00557 are both directed to engraftment of human hematopoietic cells in immunodeficient mice. Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to utilize the NOD/SCID/IL2rg-null mouse in the transplantation assay described by Ishikawa et al. with a reasonable expectation of success, at the time of the instant invention. A person of skill in the art would have been motivated to utilize the NOD/SCID/IL2rg-null mouse for engraftment, as a matter of design choice, said design choice amounting to combining prior art elements according to known methods to yield predictable results. Applicants should note that the *KSR* case forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. *KSR International Co. v. Teleflex Inc.*, 550 U.S.-, 82USPQ2d 1385 (2007).

Response to Arguments:

Applicants disagree, arguing Ishikawa and Stock No. 005557 do not teach or suggest that a newborn SCID/IL2rg-null mammal into which human-derived hematopoietic stem or precursor cells have been transplanted is able to generate all of B cells, T cells, and dendritic cells derived from the human-derived hematopoietic stem or precursor cells; or that engrafted human-derived hematopoietic stem or precursor cells in a newborn SCID/IL2rg-null mammal are able to differentiate into mature B cells, T cells and dendritic cells. Applicants' arguments have been fully considered, but are not found persuasive. As an initial matter, Applicants should note that dendritic cells are not an elected species of the invention.

In response, it should be noted that the mice utilized by Applicants in their claimed invention is NOD.Cg-*Prkdc*^{scid}IL2rg^{tm1Wjl}/Sz (Stock No: 00557, from Jackson Laboratory). Thus, Applicants' NOD/SCID/IL2rg-null mouse and that of the applied prior art are identical. As the hematopoietic stem cell recipient mice are identical, any resulting B cells and T cells generated in said mice must necessarily be identical. Thus, there is no requirement for specific teachings regarding B or T cell generation, because such would be inherent to the transplant recipient mice. As stated in MPEP 2112: The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." In re Napier, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir.1995) (affirmed a 35 U.S.C. 103 rejection based in part on inherent disclosure in one of the references). See also *In re Grasselli*, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983).

Moreover, "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

Thus, the rejection is maintained for reasons of record and the preceding commentary.

Claims 1, 2, 6 and 36 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Ishikawa et al. (Am. J. Transpl. 2:520-525, 2002), in view of mouse strain NOD.Cg-*Prkdc*^{scid}IL2rg^{tm1Wjl}/Sz (Stock No: 00557, Jackson Laboratory), as applied to claims 1, 2, 4, 5, 8, 34, 35 and 38 above, and further in view of Olive et al. (Immunol. Cell Biol. 76:520-525, 1998). The rejection set for the on pp. 6-7 of the Office action dated January 13, 2009 is maintained for reasons of record and is re-iterated as follows:

The claims embrace a newborn NOD/SCID/IL2rg-null mouse into which mature human hematopoietic cells have been transplanted, and which is able to generate IgG immunoglobulin from said human cells.

Ishikawa et al. teach long-term xenogeneic engrafting of cord blood human hematopoietic cells into newborn NOD/SCID/β2-microglobulin deficient mice (Title and Abstract). Further teaching multilineage engraftment, that included cells bearing the CD19 pan-specific B cell marker (Table 1, p. 492). The product description for stock no. 005557, discloses NOD.Cg-*Prkdc*^{scid}IL2rg^{tm1Wjl}/Sz mice as commercially available from the Jackson Laboratory

While neither Ishikawa et al. or Jackson Laboratory product description for stock no. 005557 describe detecting IgG in the recipient newborn mice, the production of human IgG in xenografted immunodeficient mice was well known in the prior art. Olive et al. describe the successful engraftment of human peripheral blood lymphocytes in SCID mice, determined by measurement of human IgG in mouse sera, that continued to increase for 8 weeks, in addition to T cell engraftment in lymphoid tissues (Title and Abstract; limitation of claims 6, 7, 36 and 37); thus curing the deficiency of IgG in Ishikawa et al. and product no. 005557

Ishikawa et al. state that the number of cells that were planted per newborn mouse is less than the larger graft size previously reported in earlier studies (second column, p. 493), thus providing the motivation to use newborn mice instead of the 8 week old mice utilized by Olive et al.

The teachings of Ishikawa et al., product stock no. 005557 and Olive et al. are all directed to engraftment of human hematopoietic cells in immunodeficient mice. Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine their respective teachings and to introduce human hematopoietic cells into newborn NOD/SCID/IL2rg-null mice to produce human T cells and IgG, with a reasonable expectation of success, at the time of the instant invention. A person of skill in the art would be motivated to use the newborn immunodeficient mouse of Ishikawa et al. for human hematopoietic cell engraftment, because such would require a smaller graft size.

Response to Arguments:

Applicants disagree, arguing claims 6 and 36 have been amended to recite "wherein the immunoglobulin comprises IgG, IgM, IgA and IgD", and Ishikawa Stock No. 005557 and Olive do not teach or suggest that a newborn SCID/IL2rg-null mammal into which human-derived

hematopoietic stem or precursor cells have been transplanted is able to generate human IgG, IgM, IgA and IgD. Applicants' arguments have been fully considered, but are not found persuasive. Applicants should again note that IgM, IgA and IgD are not the elected species of the invention; only IgG is the elected species of immunoglobulin.

Further, as indicated above, the ability to the recipient mice that are identical to Applicants' mice, to generate IgG from B cells is a feature inherent to such mice. Moreover, Olive et al. describe the successful engraftment of human peripheral blood lymphocytes in SCID mice, determined by measurement of human IgG in mouse sera.

Thus, the rejection is maintained for reasons of record and the remarks set forth above.

Conclusion

Claims 1, 2, 4, 6, 8, 34, 36 and 38 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Primary Examiner, Art Unit 1633